IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

REQUEST FOR FILING NATIONAL PHASE OF PCT APPLICATION UNDER 35 U.S.C. 371 AND 37 CFR 1.494 OR 1.495

To: Hon. Commissioner of Patents
Washington, D.C. 20231

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US)

Atty Dkt: P 0281528 /Z70481/UST
M# /Client Ref.

From: Pillsbury Winthrop LLP, IP Group:

Date: August 15, 2001

This is a **REQUEST** for **FILING** a PCT/USA National Phase Application based on:

1. International Application	2. International Filing Date	3. Earliest Priority Date Claimed
PCT/GB00/00481	15 February 2000	17 February 1999
⇧ country code	Day MONTH Year	Day MONTH Year (use item 2 if no earlier priority)

4. Measured from the earliest priority date in item 3, this PCT/USA National Phase Application Request is being filed within:

(a) ☐ 20 months from above item 3 date (b) ☒ 30 months from above item 3 date,

(c) Therefore, the due date (unextendable) is August 17, 2001

5. Title of Invention PROCESS FOR THE PRODUCTION OF TERT-BUTYL (E)-(6-[2-[4-(4-FLUOROPHENYL)-6-ISOPROPYL-2-[[METHYL (METHYLSUFONYL) AMINO] PYRIMIDIN-5-YL] VINYL] 4R, 6S)-2, 2-DIMETHYL [1, 3] DIOXAN-4-YL) ACETATE

6. Inventor(s) KOIKE, Haruo et al

Applicant herewith submits the following under 35 U.S.C. 371 to effect filing:

7. ☒ Please immediately start national examination procedures (35 U.S.C. 371 (f)).

8. ☒ **A copy of the International Application** as filed (35 U.S.C. 371(c)(2)) is transmitted herewith (file if in English but, if in foreign language, file only if not transmitted to PTO by the International Bureau) including:

a. ☒ Request;
b. ☒ Abstract;
c. 13 pgs. Spec. and Claims;
d. ___ sheet(s) Drawing which are ☐ informal ☐ formal of size ☐ A4 ☐ 11"

9. ☒ **A copy of the International Application has been transmitted by the International Bureau.**

10. **A translation of the International Application** into English (35 U.S.C. 371(c)(2))

a. ☐ Is transmitted herewith including: (1) ☐ Request; (2) ☐ Abstract;
(3) _____ pgs. Spec. and Claims;
(4) _____ sheet(s) Drawing which are:
☐ informal ☐ formal of size ☐ A4 ☐ 11"

b. ☐ Is not required, as the application was filed in English.

c. ☐ Is not herewith, but will be filed when required by the forthcoming PTO Missing Requirements Notice per Rule 494(c) if box 4(a) is X'd or Rule 495(c) if box 4(b) is X'd.

d. ☐ Translation verification attached (not required now).

11. ☒ Please see the attached Preliminary Amendment

12. ☐ Amendments to the claims of the International Application **under PCT Article 19 (35 U.S.C. 371(c)(3)), i.e., before 18th month from first priority date above in item 3, are transmitted herewith (file only if in English) including:**

13. ☒ PCT Article 19 claim amendments (if any) have been transmitted by the International Bureau

14. ☐ Translation of the amendments to the claims **under PCT Article 19 (35 U.S.C. 371(c)(3)), i.e., of claim amendments** made before 18th month, **is attached (required by 20th month from the date in item 3 if box 4(a) above is X'd, or 30th month if box 4(b) is X'd, or else amendments will be considered canceled).**

15. **A declaration of the inventor** (35 U.S.C. 371(c)(4))
a. ☐ is submitted herewith ☐ Original ☐ Facsimile/Copy
b. ☒ is not herewith, but will be filed when required by the forthcoming PTO Missing Requirements Notice per Rule 494(c) if box 4(a) is X'd or Rule 495(c) if box 4(b) is X'd.

16. **An International Search Report (ISR):**
a. Was prepared by ☒ European Patent Office ☐ Japanese Patent Office ☐ Other
b. ☒ has been transmitted by the international Bureau to PTO.
c. ☒ Copy herewith (2 pg(s).) ☒ plus Annex of family members (1 pg(s).).

17. **International Preliminary Examination Report** (IPER):
a. ☒ Has been transmitted (if this letter is filed after 28 months from date in item 3) in English by the International Bureau with Annexes (if any) in original language.
b. [X] Copy herewith in English.
c.1 ☐ IPER Annex(es) in original language ("Annexes" are amendments made to claims/spec/drawings during Examination) including attached amended:
c.2 ☐ Specification/claim pages #___ claims #
Dwg Sheets #
d. ☐ Translation of Annex(es) to IPER **(required by 30th month due date, or else annexed amendments will be considered canceled).**

18. **Information Disclosure Statement** including:
a. [X] Attached Form PTO-1449 listing documents
b. ☐ Attached copies of documents listed on Form PTO-1449
c. ☒ A concise explanation of relevance of ISR references is given in the ISR.

19. ☐ **Assignment** document and Cover Sheet for recording are attached. Please mail the recorded assignment document back to the person whose signature, name and address appear at the end of this letter.

20. ☐ Copy of Power to IA agent.

21. ☐ **Drawings** (complete only if 8d or 10a(4) not completed): __ sheet(s) per set: ☐ 1 set informal; ☐ Formal of size ☐ A4 ☐ 11"

22. Small Entity Status ☒ is **Not** claimed ☐ is claimed (**pre**-filing confirmation required)
22(a) ___ (No.) Small Entity Statement(s) enclosed (since 9/8/00 Small Entity Statements(s) not essential to make claim)

23. **Priority** is hereby claimed under 35 U.S.C. 119/365 based on the priority claim and the certified copy, both filed in the International Application during the international stage based on the filing in (country) GREAT BRITAIN of:

	Application No.	Filing Date		Application No.	Filing Date
(1)	9903472.0	February 17, 1999	(2)		
(3)			(4)		
(5)			(6)		

a. ☒ See Form PCT/IB/304 sent to US/DO with copy of priority documents. If copy has not been received, please proceed promptly to obtain same from the IB.
b. ☐ Copy of Form PCT/IB/304 attached.

RE: USA National Phase Filing of PCT/GB00/00481

24. Attached: 2 pages of Form PCT/IB/306

25 Per Item 17.c2, **cancel original** pages #___, claims #___, Drawing Sheets #

26. **Calculation of the U.S. National Fee (35 U.S.C. 371 (c)(1)) and other fees is as follows:**
Based on amended claim(s) per above item(s) ☐ 12, ☐ 14, ☐ 17, ☐ 25 (hilite)

Total Effective Claims	minus 20 =	x $18/$9	=	$0	966/967
Independent Claims	minus 3 =	x $80/$40	=	$0	964/965
If any proper (ignore improper) Multiple Dependent claim is present,		add$270/$135		+0	968/969

BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(4)): →→ **BASIC FEE REQUIRED, NOW** →→→→

A. If country code letters in item 1 are **not** "US","BR","BB","TT","MX","IL" "NZ", "IN" or "ZA"

See item 16 re:

1.	Search Report was not prepared by EPO or JPO - - - - - - - - -	add$1000/$500		960/961
2.	Search Report was prepared by EPO or JPO - - - - - - - - - - - -	add$860/$430	+860	970/971

SKIP B, C, D AND E UNLESS country code letters in item 1 are "US","BR","BB","TT","MX","IL", "NZ", "IN" or "ZA"

(X) →	☐	B.	If USPTO did not issue both International Search Report (ISR) and (if box 4(b) above is X'd) the International Examination Report (IPER), - - - - - - - - - - - - - - - - - - -	add$1000/$500	+0	960/961
(only) (one) → (of)	☐	C.	If USPTO issued ISR but not IPER (or box 4(a) above is X'd), -	add$710/$355	+0	958/959
(these) (7) → (boxes)	☐	D.	If USPTO issued IPER but IPER Sec. V boxes not all 3 YES, -	add$690/$345	+0	956/957
→	☐	E.	If international preliminary examination fee was paid to USPTO and Rules 492(a)(4) and 496(b) satisfied (IPER Sec. V all 3 boxes YES for all claims), - - - - - - - - - - - - -	add $100/$50	+0	962/963

27. **SUBTOTAL =** $860

28. If Assignment box 19 above is X'd, add Assignment Recording fee of ----$40 +0 (581)

29. Attached is a check to cover the - **TOTAL FEES** $860

Our Deposit Account No. 03-3975
Our Order No. 009901 (C#) | 0281528 (M#)

00909

CHARGE STATEMENT: The Commissioner is hereby authorized to charge any fee specifically authorized hereafter, or any missing or insufficient fee(s) filed, or asserted to be filed, or which should have been filed herewith or concerning any paper filed hereafter, and which may be required under Rules 16-18 and 492 (missing or insufficient fee only) now or hereafter relative to this application and the resulting Official document under Rule 20, or credit any overpayment, to our Account/Order Nos. shown above for which purpose a duplicate copy of this sheet is attached.
This CHARGE STATEMENT does not authorize charge of the issue fee until/unless an issue fee transmittal form is filed

Pillsbury Winthrop LLP
Intellectual Property Group

By Atty: Donald J. Bird **Reg. No.** 25323

Sig: _____ **Fax:** (703) 905-2500
Tel: (703) 905-2018

Atty/Sec: DJB/mhn

NOTE: File in duplicate with 2 postcard receipts (PAT-103) & attachments.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION OF

Inventor(s): KOIKE, Haruo et al

Filed: Herewith

Title: PROCESS FOR PRODUCTION OF TERT-BUTYL (E)-(6-[2-[4- (4-FLUOROPHENYL)-6-ISOPROPYL-2-[METHYL(METHYLSULFONYL) AMINO] PYRIMIDIN-5-YL] VINYL] (4R,6S)-2,2-DIMETHYL [1, 3] DIOXAN-4-YL) ACETATE

August 15, 2001

PRELIMINARY AMENDMENT

Hon. Commissioner of Patents
Washington, D.C. 20231

Sir:

Please amend this application as follows:

IN THE SPECIFICATION:

At the top of the first page, just under the title, insert

☒ --This application is the National Phase of International Application PCT/GB00/00481 filed February 15, 2000 which designated the U.S. and that International Application

☒ was ☐ was not published under PCT Article 21(2) in English.--

Respectfully submitted,

PILLSBURY WINTHROP LLP
Intellectual Property Group

By: _____

Attorney: Donald J. Bird
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09/913539
518 Rec'd PCT/PTO 15 AUG 2001

APPLICATION UNDER UNITED STATES PATENT LAWS

Atty. Dkt. No. PW 0281528/Z70481/UST
(M#)

Invention: PROCESS FOR THE PRODUCTION OF TERT-BUTYL (E)-(6-[2-[4-(4-FLUOROPHENYL)-6-ISOPROPYL-2-[METHYL (METHYLSULFONYL) AMINO] PYRIMIDIN-5-YL] VINYL] (4R, 6S)-2, 2-DIMETHYL [1, 3] DIOXAN-4-YL) ACETATE

Inventor (s): KOIKE, Haruo
KABAKI, Mikio
TAYLOR, Nigel Philip
DIORAZIO, Louuis Joseph

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McLean, VA 22102
Attorneys
Telephone: (703) 905-2000

09913539.120701

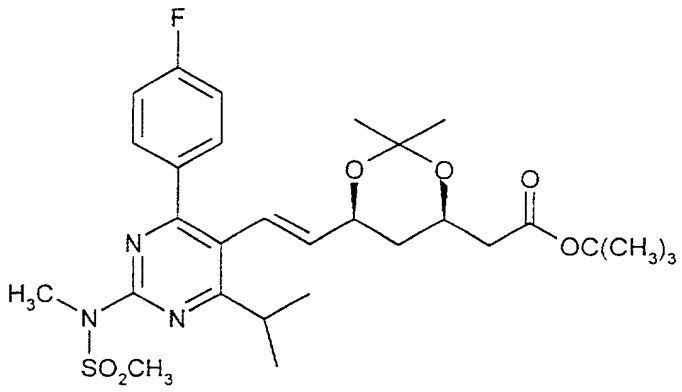
This is a:

- ☐ Provisional Application
- ☐ Regular Utility Application
- ☐ Continuing Application
  - ☒ The contents of the parent are incorporated by reference
- ☒ PCT National Phase Application
- ☐ Design Application
- ☐ Reissue Application
- ☐ Plant Application
- ☐ Substitute Specification
  Sub. Spec Filed ________
  in App. No. ____ / ____
- ☐ Marked up Specification re
  Sub. Spec. filed ________
  In App. No ____ / ____

SPECIFICATION

PROCESS FOR THE PRODUCTION OF TERT-BUTYL (E)-(6-[2-[4-(4-FLUOROPHENYL)-6-ISOPROPYL-2-[METHYL(METHYLSULFONYL)AMINO]PYRIMIDIN-5-YL]VINYL](4R,6S)-2,2-DIMETHYL[1,3]DIOXAN-4-YL)ACETATE

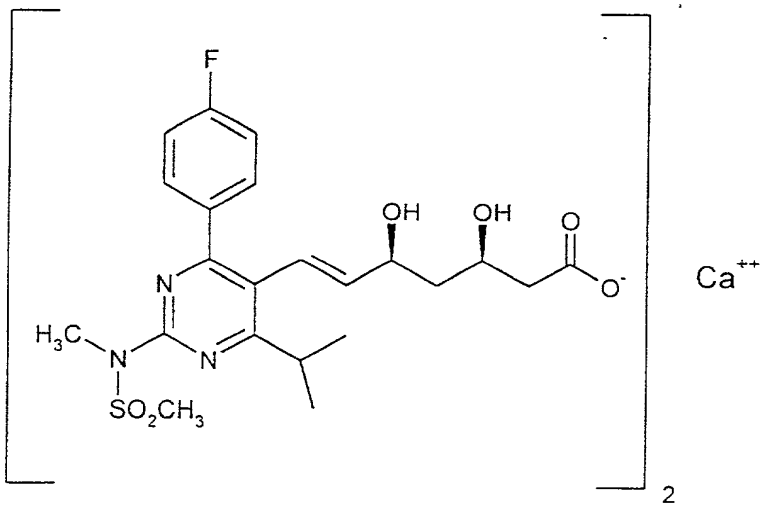
This invention concerns a novel chemical process, and more particularly it concerns a novel chemical process for the manufacture of tert-butyl (E)-(6-{2-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]vinyl}(4R,6S)-2,2-dimethyl[1,3]dioxan-4-yl)acetate of formula I,



Formula I

(hereinafter referred to as BEM) which is useful, for example, as a chemical intermediate in the production of a pharmaceutical useful in the treatment of, inter alia, hypercholesterolemia, hyperlipoproteinemia and atherosclerosis. The invention further includes the novel starting material used in said process and the use of the process in the manufacture of an HMG CoA reductase inhibitor.

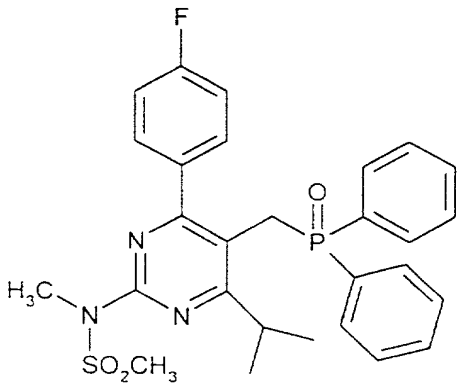
In European Patent Application, Publication No. (EPA) 0521471 is disclosed (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid and its sodium salt and calcium salt (illustrated below)



(hereinafter referred to collectively as "The Agent") as inhibitors of HMG CoA reductase. The Agent is obtained therein via reduction of methyl 7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonyl-amino)pyrimidin-5-yl-(3R)-3-hydroxy-5-oxo-(E)-heptenoate and subsequent processing. However the Agent may be obtained from BEM by treatment with acid (to cleave the acetonide protecting group) followed by base (to cleave the ester) and (as described in EPA 0521471) conversion of the initially formed salt to the free acid or the calcium salt.

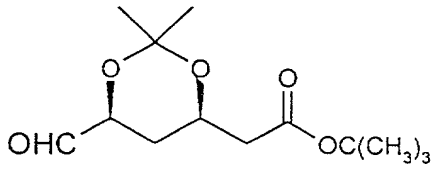
We have now discovered a useful and advantageous process for preparing BEM.

According to the invention there is provided a process for preparing BEM (formula I) which comprises reaction of diphenyl [4-(4-fluoropheny)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-ylmethyl] phosphine oxide of formula III ·



Formula III

(hereinafter referred to as DPPO) with tert-butyl 2-[(4R,6S)-6-formyl-2,2-dimethyl-1,3-dioxan-4-yl}acetate of formula II



Formula II

(hereinafter referred to as BFA) in the presence of a strong base.

The process is carried out in a suitable solvent, or mixture of solvents for example, ethereal or aromatic solvents or mixtures thereof. Particularly suitable solvents include, for example, tetrahydrofuran (THF), dimethoxyethane and toluene, or mixtures thereof. Particularly preferred solvents include, for example, THF and THF and toluene.

Suitable bases for use in the process include, for example, amide bases, alkyl metals and metal hydrides. Particular bases include, for example, sodium bis(trimethylsilyl)amide, potassium bis(trimethylsilyl)amide, lithium bis(trimethysilyl)amide, butyllithium and sodium hydride. A particularly preferred base is, for example, sodium bis(trimethylsilyl)amide (NaHMDS).

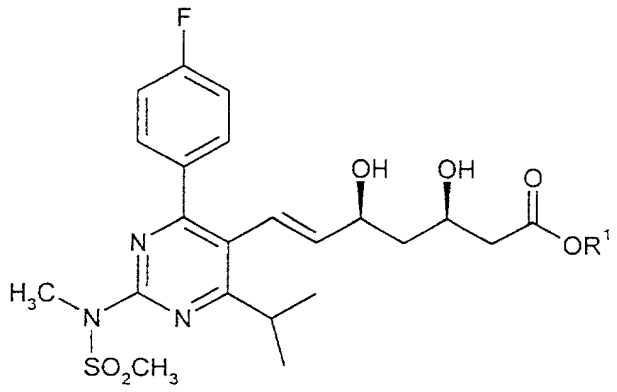
The reaction may be carried out at a temperature in the range of, for example, -20°C to -90°C, such as -40°C to -90°C, for example -40°C to -80°C. A convenient temperature at which to carry out the reaction is, for example, that of a mixture of acetone and solid carbon dioxide (about -75°C).

The process is advantageously carried out with 1.0 to 1.2 equivalents of base (per equivalent of DPPO), such as 1.05 to 1.2 equivalents and preferably 1.05 to 1.12 equivalents. Although BFA can be present in large excess, it is convenient to use 1.0 to 1.35 equivalents (per equivalent of DPPO), and preferably 1.05 to 1.3 equivalents, especially 1.05 to 1.15 equivalents.

The process of the invention provides significantly improved yields and quality of product by comparison to when a corresponding dialkyl phosphonate (-$PO(Oalkyl)_2$) starting material is used instead of DPPO.

The starting material, DPPO, which is a further aspect of the present invention, may be obtained as described in the Examples hereinafter, starting from an alkyl 2-amino-4-(4-fluorophenyl)-6-isopropylpyrimidin-5-carboxylate, for example the methyl ester which may be obtained as described in Japanese Patent Application No. 06-256318, or the ethyl ester which may be obtained as described in EPA 0521471. BFA may be obtained as described in EPA 0319847 (Example 6).

A further aspect of the present invention is a process for the manufacture of a compound of the formula IV



Formula IV

in which R^1 is hydrogen or a pharmaceutically acceptable cation, which comprises;

(1) reaction of DPPO with BFA in the presence of a strong base (as described above) to give BEM;

(2) cleavage of the dihydroxy (acetonide) protecting group (for example by acid hydrolysis, such as by using HCl in THF or acetonitrile); and

(3) cleavage of the tert-butyl ester group under basic conditions to form a compound of the formula IV in which R^1 is a pharmaceutically acceptable cation (for example by using a solution of a metallic hydroxide in a polar solvent, such as using aqueous sodium hydroxide in ethanol or acetonitrile to form the sodium salt);

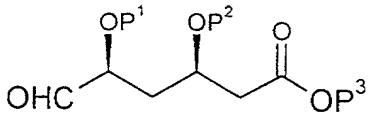
optionally followed by neutralisation to give a compound of the formula IV in which R^1 is hydrogen;

and/or optionally followed by conversion to another compound of the formula IV in which R^1 is a pharmaceutically acceptable cation (for example conversion of the sodium salt to the

calcium salt by treatment with a water soluble calcium salt (such as calcium chloride) under aqueous conditions).

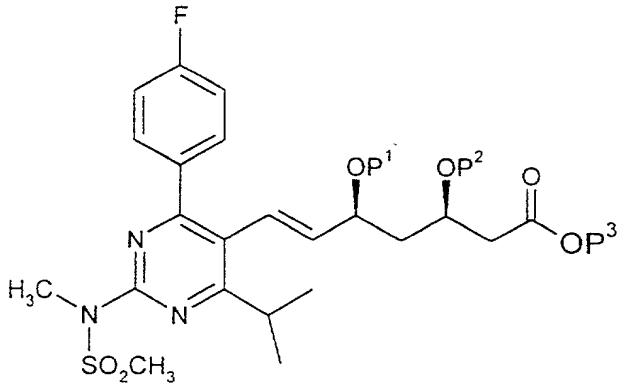
Suitable conditions for steps (2), (3) and the subsequent optional steps are analogous to, or the same as, those disclosed in EPA 0521471 and/or EPA 0319847, which are hereby incorporated herein by reference. To obtain the calcium salt of the compound of formula IV, as illustrated on page 1, preferably steps (2), (3) and conversion to the calcium salt via the methylamine salt are carried out as described in Example 7, which steps form a further aspect of the invention.

It will be appreciated that, in the processes described above, BFA may be replaced by a compound of the general formula V



Formula V

in which P^1 and P^2 are alcohol protecting groups, or P^1 and P^2 taken together is a 1,3-diol protecting group, such as those described in EPA 0319847 and GB 2244705 which are included herein by reference, and P^3 is a carboxylic acid protecting group, for example (1-8C)alkyl (such as (1-4C)alkyl), to form a compound of the formula VI



Formula VI

The compound of the formula VI may be converted to the Agent by cleavage of the alcohol or diol protecting groups and conversion of the $COOP^3$ to a COOH group or a pharmaceutically acceptable salt thereof. Such general processes form further features of the present invention.

The invention is further illustrated, but not limited by the following Examples.

Preparation 1

Preparation of DPPO

A stirred mixture of methyl 4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidine-5-carboxylate (12.0 g) in toluene (55ml) was cooled to -10°C and diisobutyl aluminium hydride (50 ml of a 1.5M solution in toluene) was added over two hours maintaining the temperature below 0°C. After addition, the mixture was stirred for 30 minutes at 0°C. Methanol (0.64 ml) was added to the mixture maintaining the temperature at 0°C. The mixture was then added over two hours to a stirred mixture of concentrated hydrochloric acid (23.3 ml), water (40.5 ml) and acetonitrile (24 ml) at 40°C, maintaining the temperature of the mixture at 40°C. After addition, the mixture was stirred at 40°C for a further 30 minutes and then purged with nitrogen (to remove any isobutane). The mixture was cooled to 20°C and allowed to stand for 20 minutes. The organic phase was separated and washed with a mixture of concentrated hydrochloric acid (0.7 ml) and water (30 ml). Acetonitrile (24 ml) was added to the organic phase and the mixture washed with a solution of sodium bicarbonate (0.038 g) in water (120 ml).

The organic phase was heated to 40°C, and then from 40°C to 80°C using a nitrogen purge. The mixture was concentrated by distillation at atmospheric pressure, collecting 54 ml of distillate. Acetonitrile (24 ml) was added to the concentrated solution and phosphorus tribromide (1.2 ml) was added with stirring, maintaining the temperature of the mixture at 20°C. After addition, the mixture was stirred at 20°C for 30 minutes. The mixture was added to water (36 ml) over 30 minutes maintaining the temperature at 20°C. The mixture was stirred for 5 minutes and the organic phase separated. The organic phase was washed with a solution of sodium bicarbonate (0.027 g) in water (36 ml), followed by water (36 ml). The organic phase was distilled under reduced pressure until 29 ml of distillates was collected. The mixture was cooled to 60°C and ethyl diphenylphosphinite (7.47 ml) was added. The mixture was stirred at 60°C for 3 hours, then heated to reflux. Toluene (40 ml) was added and the mixture cooled to 0°C over 2 hours. The product was collected by filtration, washed with cold toluene (10 ml) and dried under vacuum at 50°C to give DPPO (14.66 g); ^{1}HNMR ($CDCl_3$, 270 MHz): 7.42 [m, 10H, $P(C_6\underline{H}_5)_2$], 7.12 [m, 2H, Ar-H], 6.92 [m, 2H, Ar-H], 3.92 [d,2H, $C\underline{H}_2P$], 3.51, 3.46 (2 x s, 6H, $NC\underline{H}_3$ $SO_2C\underline{H}_3$], 3.43 [hept., 1H, $C\underline{H}(CH_3)_2$], 1.25 [d, 6H, $CH(C\underline{H}_3)_2$]

Methyl 4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino)pyrimidine-5-carboxylate was prepared as follows:

A mixture of methyl 2-amino-4-(4-fluorophenyl)-6-isopropyl-pyrimidine-5-carboxylate (19.0 g), sodium tert-pentoxide (22.95 g) and dimethoxyethane (190 ml) was stirred for 30 minutes at 25°C. The stirred mixture was cooled to -10°C and methanesulfonyl chloride (8.4 ml) was added dropwise, maintaining the temperature of the mixture at -5°C. After 20 minutes, dimethyl sulfate (8.1 ml) was added and the mixture allowed to warm to 25°C. The mixture was stirred for one hour at 25°C and a solution of sodium tert-pentoxide (1.91 g) in dimethoxyethane (10 ml) added. The mixture was stirred for one hour at 25°C. A solution of sodium chloride (13.3 g) in water (133 ml) was added and the mixture was stirred for 10 minutes at 25°C. The mixture was allowed to settle for 15 minutes and the lower aqueous phase was separated and discarded. Water (38 ml) was added to the remaining mixture and the mixture was stirred for 30 minutes at 25°C. The mixture was then heated to obtain a complete solution. The mixture was cooled slowly to 25°C over one hour. The mixture was cooled to 0°C, stirred for one hour, and the suspended solid collected by filtration. The solid was washed with cold (0°C) solution of 50:50 water/dimethoxyethane (20 ml). The solid was dried under vacuum at 60°C to give methyl 4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidine-5-carboxylate (19.35 g); ^{1}HNMR (270 MHz, $CDCl_3$): 7.69 (m,2H), 7.14 (m,2H), 3.71, 3.60, 3.51 (3 x s, 9H), 3.20 (m, 1H), 1.32 (d,6H).

Example 1

A mixture of DPPO (19.17 g) and THF (227 ml) were warmed briefly to 40°C until a clear solution had formed then inerted by the sequential application of vacuum and nitrogen (5 cycles). The mixture was immersed in an acetone/CO_2 bath cooling the contents to -75°C. Sodium bis(trimethylsilyl)amide (37.4 ml of 1.0M solution in THF) was added to the reaction mixture over 10 minutes from a pressure equalising dropping funnel maintaining the temperature below -74°C and forming a red solution of the anion. THF (10 ml) was rinsed through the dropping funnel into the mixture and the mixture stirred a further 1 hour at -76°C forming a red suspension. BFA (80 ml of ~13.5% w/w toluene solution) was added in portions to the suspension over 20 minutes from a pressure equalising dropping funnel maintaining the temperature below -73°C. Toluene (20 ml) was rinsed through the dropping

funnel into the mixture and the mixture stirred a further 15 minutes at -76°C. The chilling bath was lowered and the suspension allowed to warm to 10°C over 1.5 hours. Glacial acetic acid (3.21 g) in water (15 g) was added in one portion raising the temperature to 18°C and dissolving all solids and the mixture was stirred a further 5 minutes.

The mixture was concentrated by distillation at atmospheric pressure (jacket 110°C) to a temperature of 94°C collecting a total of 274 ml distillates. The concentrated mixture was cooled to 40°C, water (40 ml) was added and the mixture stirred for 5 minutes then allowed to settle for 15 minutes. The lower aqueous phase was discarded. Sodium hydrogen carbonate (2.99 g) in water (40 ml) was added and the mixture stirred for 5 minutes then allowed to settle for 15 minutes. The lower aqueous phase was discarded. Water (30 ml) was added and the mixture stirred for 5 minutes then allowed to settle for 15 minutes. The lower aqueous phase was discarded.

The organic phase was transferred to a distillation apparatus with toluene (20 ml) and concentrated by distillation at atmospheric pressure (jacket 125-130°C) to a temperature of 116°C collecting 85 ml distillates. Vacuum was applied (400-500 mbar) and a further 16.5 ml distillates collected to a temperature of 111°C. The vacuum was released and the concentrated mixture allowed to cool to 80°C. Warm MeOH (140 ml, 50°C) was added with rapid stirring and the batch allowed to self-cool to 20°C over 30 minutes during which time a solid was deposited. The suspension was further cooled to 2°C for 30 minutes then the solid was collected by filtration on a sinter and pulled as dry as possible. The solid was washed with cold MeOH (60 ml, 2°C) and again pulled as dry as possible then transferred to a vacuum oven and dried overnight (50°C, 200 mbar); giving BEM (14.01 g, 67.7%).

^{1}H NMR ($CDCl_3$, 270 MHz)

7.65 [m, 2H, Ar-H], 7.09 [m, 2H, Ar-H], 6.52 [dd, 1H, ArCH=CH], 5.47 [dd, 1H, ArCH=CH], 3.57, 3.50 [2 x s, 6H, NCH_3, SO_2CH_3], 3.38 [hept., 1H, Ar-$CHMe_2$], 2.45, 2.30 [2 x dd, 2H, CH_2CO_2tBu], 1.55, 1.13 [dt, dd, 2H, acetonide CH_2], 1.50, 1.40 [2 x s, 6H, acetonide $C(CH_3)_2$], 1.45 [s, 9H, $CO_2C(CH_3)_3$], 1.27 [dd, 6H, $ArCH(CH_3)_2$]

Examples 2-6

The procedure as described in Example 1 was carried out using the ratios of reactants and the temperatures given in Table 1 There was thus obtained BEM in the yields given

Table 1

Wt DPPO	Temp. (°C)	Eq. NaHMDS	Eq. BFA	BEM Yield
10.00 g	-75	1.12	1.20	69.2%
18.12 g	-75	1.12	1.20	69.6%
12.08 g	-75	1.06	1.26	72.8%
19.17 g	-40	1.05	1.06	56.7%
9.57 g	-90	1.05	1.10	72.0%
9.57 g	-60	1.05	1.10	70.1%

Example 7

A mixture of BEM (5.0 g) and acetonitrile (35 ml) was stirred under an inert atmosphere at 40°C. 0.02M hydrochloric acid (9.5 ml) was added over 30 minutes to the resultant solution, maintaining the temperature at 35°C to 42°C. The mixture was stirred at 40°C for 3 hours then cooled to 25°C. 1.0M sodium hydroxide solution (9.5 ml) was added with stirring at 25°C and the mixture was stirred for an additional one hour at 25°C. Sodium chloride (4.7 g) was added and the mixture was cooled to -5°C over one hour. Sufficient of a solution of 1M hydrochloric acid (9.5 ml) and sodium chloride (2.4 g) was added at -5°C to achieve a pH of 3.4 to 4.0 and the mixture stirred at this temperature for 5 minutes. The mixture was allowed to settle for 10 minutes at -5°C to give two layers. The lower layer was separated and discarded. Acetonitrile (65 ml) at -5°C was added to the remaining solution and the mixture was filtered through a filter agent. 40% methylamine solution in water (1.1 ml) was added at -5°C and the mixture was warmed to 30°C over 40 minutes and maintained at this temperature for 90 minutes. The mixture was then cooled to 0°C over 40 minutes and maintained at this temperature for 90 minutes. The resultant solid was collected by filtration and washed with acetonitrile (2x12 ml). The solid, which is the methylamine salt of the compound of formula IV ($R^1 = MeNH_3^+$), was dried under vacuum at 35°C (3.87 g). 8% w/w aqueous sodium hydroxide (5.44 ml) was added to a stirred mixture of the methylamine salt (6.0 g) in degassed water (30 ml) at 20°C and the mixture was stirred for one hour. The mixture was filtered and concentrated under reduced pressure at 40°C until 24 ml of distillate collected. Water (24 ml) was added and the mixture again concentrated under reduced

pressure at 40°C until 24 ml of distillate collected. Water (30 ml) was added and a solution of calcium chloride dihydrate (1.03 g) in water (6 ml) was added dropwise at 20°C. The mixture was stirred for 45 minutes and the resultant solid filtered. The solid was washed with water (36 ml) and dried under vacuum at 40°C to give the calcium salt of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid.

Claims

1. A process for the manufacture of tert-butyl (E)-(6-{2-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]vinyl}-(4R,6S)-2,2-dimethyl[1,3]dioxan-4-yl)acetate which comprises reaction of diphenyl [4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-ylmethyl]phosphine oxide with tert-butyl 2-[(4R,6S)-6-formyl-2,2-dimethyl-1,3-dioxan-4-yl]acetate in the presence of a strong base.

2. A process as claimed in claim 1 wherein the reaction is carried out at a temperature in the range of -20°C to -90°C.

3. A process as claimed in claim 1 or 2 wherein the strong base is sodium bis(trimethylsilyl)amide.

4. A process as claimed in claim 1, 2 or 3 wherein the reaction is carried out in a solvent selected from tetrahydrofuran, dimethoxyethane and toluene, and mixtures thereof.

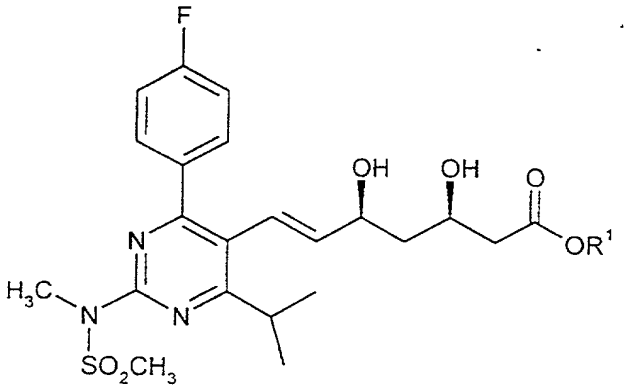
5. A process as claimed in any of claims 1 to 4 wherein 1.0 to 1.2 equivalents of base are used per equivalent of the phosphine oxide.

6. A process as claimed in any of claims 1 to 5 wherein 1.0 to 1.35 equivalents of tert-butyl 2-[(4R,6S)-6-formyl-2,2-dimethyl-1,3-dioxan-4-yl]acetate are used per equivalent of the phosphine oxide.

7. The compound diphenyl [4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-ylmethyl]phosphine oxide.

8. The compound tert-butyl (E)-(6-{2-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]vinyl}-(4R,6S)-2,2-dimethyl[1,3]dioxan-4-yl)acetate.

9. A process for the manufacture of a compound of the formula IV



Formula IV

in which R^1 is hydrogen or a pharmaceutically acceptable cation which comprises

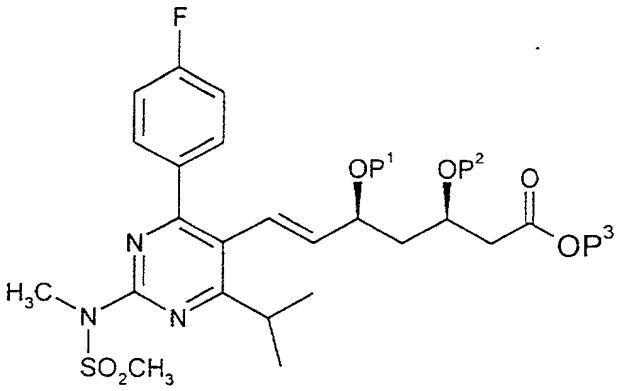
(1) reaction of diphenyl [4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-ylmethyl]phosphine oxide with tert-butyl 2-[(4R, 6S)-6-formyl-2,2-dimethyl-1,3-dioxan-4-yl]acetate in the presence of a strong base to give tert-butyl (E)-(6-{2-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]-pyrimidin-5-yl]vinyl}(4R,6S)-2,2-dimethyl[1,3]dioxan-4-yl)acetate of formula I;

(2) cleavage of the dihydroxy protecting group from the product of step (1);

(3) cleavage of the tert-butyl ester group under basic conditions from the product of step (2) to form a compound of the formula IV in which R^1 is a pharmaceutically acceptable cation;

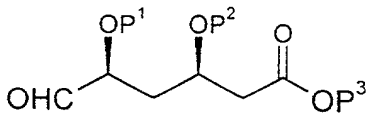
optionally followed by neutralisation to give a compound of the formula IV in which R^1 is hydrogen; and/or optionally followed by conversion to another compound of the formula IV in which R^1 is a pharmaceutically acceptable cation.

10. A process for the manufacture of a compound of the formula VI



Formula VI

which comprises reaction of diphenyl [4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-ylmethyl]phosphine oxide with a compound of the formula V



Formula V

in the presence of a strong base, wherein P^1 and P^2 are alcohol protecting groups, or P^1 and P^2 taken together is a 1,3-diol protecting group, and P^3 is a carboxylic acid protecting group.

FOR UTILITY/DESIGN
CIP/IPCT NATIONAL/PLANT
ORIGINAL/SUBSTITUTE/SUPPLEMENTAL
DECLARATIONS

RULE 63 (37 C.F.R 1.63)
DECLARATION AND POWER OF ATTORNEY
FOR PATENT APPLICATION
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PW
FORM
Z70481/UST

As a below named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name, and I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the INVENTION ENTITLED: PROCESS FOR THE PRODUCTION OF TERT-BUTYL(E)-(6-[2-[4[(4-FLUOROPHENYL)-6-ISOPROPYL-2-[METHYL (METHYLSULFONYL)AMINO]PYRIMIDIN-5-YL] VINYL(4R,6S)-2,2-DIMETHYL[1,3]DIOXAN-4-YL)ACETATE

the specification of which (CHECK applicable BOX(ES))

X BOX(ES)
A. ☐ is attached hereto.
→ B. ☐ was filed on _____ as U S Application No._____
→ → C. ☐ was filed as PCT International Application No. PCT/ GB00/00481 On 15 February 2000

and (if applicable to U.S. or PCT application) was amended on _____ I hereby state that I have reviewed and understand the contents of the above identified specification. including the claims, as amended by any amendment referred to above I acknowledge the duty to disclose all information known to me to be material to patentability as defined in 37 C.F.R. 1.56. Except as noted below, I hereby claim foreign priority benefits under 35 U.S.C. 1 19(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate. or 365(a) of any PCT International Application which designated at least one other country than the United States, listed below and have also identified below any foreign application for patent or inventor's certificate, or PCT International Application, filed by me or my assignee disclosing the subject matter claimed in this application and having a filing date (1) before that of the application on which priority is claimed. or (2) if no priority claimed, before the filing date of this application.

PRIOR FOREIGN APPLICATION(S) Number	Country	Day/MONTH/Year Filed	Date first laid-open or Published	Date Patented or Granted	Priority NOT Claimed
9903472.0	United Kingdom	17 February 1999			

Except as noted below, I hereby claim domestic priority benefit under 35 U.S.C 119(e) or 120 and/or 365(c) of the indicated United States applications listed below and PCT international applications listed above or below and, if this is a continuation-in-part (CIP) application, insofar as the subject matter disclosed and claimed in this application is in addition to that disclosed in such prior applications, I acknowledge the duty to disclose all information known to me to be material to patentability as defined in 37 C.F.R 1 56 which became available between the filing date of each such prior application and the national or PCT international filing date of this application:

PRIOR U.S. PROVISIONAL, NON PROVISIONAL AND/OR PCT APPLICATION(S) Application No. (series code/serial no.)	Day/MONTH/Year Filed	Status Pending, abandoned, patented	Priority NOT Claimed

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 16 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

And I hereby appoint Pillsbury Winthrop LLP, Intellectual Property Group, telephone number (202)861-3000 (to whom all communications are to be directed), and persons of that firm who are associated with USPTO Customer No.909 (see below label) individually and collectively my attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith and with the resulting patent, and I hereby authorize them to delete from that Customer No. names of persons no longer with their firm, to add new persons of their Firm to that Customer No., and to act and rely on instructions from and communicate directly with the person/assignee/attorney/firm/organization who/which first sends/sent this case to them and by whom/which I hereby declare that I have consented after full disclosure to be represented unless/until I instruct the above Firm and/or an attorney of that Firm in writing to the contrary.

00909

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☐ See additional foreign i,riorities on attached page (incorporated herein by reference).

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Z70481/UST

DECLARATION AND POWER OF ATTORNEY
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